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14. ABSTRACT

A high proportion of breast cancer cases in the Philippines and in developing countries in general present at advanced stages and have a rapid unfavorable outcome. Many of these cases could have a good prognosis if detected earlier. This was an intervention study to assess the feasibility and efficacy of screening by Clinical Breast Examination (CBE) in reducing mortality from breast cancer. Women resident in 12 municipalities of Manila were offered CBE performed by trained nurses, if detected positive they were referred to tumor clinics set up for the management of project cases. Though screening was well received, only 40% of women detected positive reported to the tumour clinics. The cost of treatment, lack of trust in the health system and fear of a disease still largely perceived as fatal, were the main reasons given to refuse clinical follow up. This is a reminder that when introducing community screening in developing countries specific culturally-related health-belief issues need also to be addressed. Nevertheless, the project also showed that good quality management could be provided with affordable and sustainable investments and that improved management can have a significant impact on clinical outcome. The median survival of screened-detected cases was significantly greater than median survivals of refusers and of symptomatic cases diagnosed in the control areas. A health system capable of improving survival will contribute to the credibility of awareness campaigns and help to change the negative attitude of the population.

15. SUBJECT TERMS
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Table of Contents

Note:

The Statement of Work approved with the application was applied in the first 3 years of the project. In 1997, in view of the interim results, we proposed a modification of the Statement of Work that was approved in 1998. The revised Statement of Work supersedes the previous from project year 4.

Statement of Work and Revised Statement of Work are copied in Annex 1.

Reference to the Statements of Work is indicated within the text in the Material and Methods.

Introduction

In recent years research on means to improve cancer control when resources are limited has focused on the evaluation of low-cost screening procedures and this study is an example in this direction. The outcome of this trial proves however, that culturally-related health beliefs are a major obstacle to early diagnosis. Access to health care and trust need to be addressed in first place.

In year 2000 breast cancer accounted for over 1 million new cases per year worldwide; it is the most common cancer in women, and incidence rates are still rising, particularly in low-risk countries[1]. These trends are likely to continue, since the current pattern of later childbearing, decreasing fertility, increasing height and weight and 'westernization' of diets will all be associated with increased risk.

Significant improvements in the prognosis of early breast cancer have been achieved in the 80s and 90s[2,3] and are believed to be a major cause of the initial reduction of mortality observed in some high-risk countries[4, 5, 6, 7]. For treatment to be highly effective however, it is essential that the disease is detected at an early clinical stage.

Mammography is an expensive technology that requires highly trained radiologists and radiographers. It can reduce breast cancer mortality by 25% in women 50-69 years of age[8] if participation rates and the sensitivity of the test are high, screen-positive women undergo accurate diagnostic investigation, and detected cases receive optimal treatment. The cost per life-year saved, having to meet all the conditions described above, is therefore relatively high[9,10,11] and clearly an inappropriate use of health care resources for many low-income countries[12].

Other screening strategies that have been proposed are clinical examination of the breasts (CBE), and breast self-examination (BSE).

At present CBE has never been used as the sole modality of screening in a randomised controlled trial, so that its efficacy is not known.

The study in the Philippines aimed to establish 1) whether a programme of mass screening by CBE performed by trained paramedical personnel could be set up in a developing country as part of the routine activity of first level health services, and 2) whether and to what extent such a programme could reduce mortality from breast cancer.

The study area was 12 municipalities of the Greater Manila area, the population of which had a relatively high incidence of breast cancer; the age standardized incidence in 1988-1992 was 47.7 per 10^5, a rate considerably above that of other Asian populations. Five year later the recorded rate had increased to 54.2 per 100,000 [19].

The planned project was anticipated to last 7-10 years, and to involve 5 rounds of screening for women in the intervention group, at intervals of 1-2 years. However, all attempts to motivate lump-positive women to pursue diagnosis and treatment failed. The intervention ceased therefore after completion of the first screening round.

In this paper we describe the study population, the screening intervention, and its results in terms of breast cancer detection and cumulative incidence by December 1999 (on average 3 years of follow-up) in the two groups.

Materials and methods

Study design. The study was designed as a randomised controlled trial of the effect of five annual clinical examinations of the breasts (BCE) performed by trained nurses/midwives, in reducing mortality from breast cancer. Women aged 35-64 years, resident in the central, more urbanized municipalities of the National Capital Region of Manila were the target population. The intervention included women below age 40 years because in a young population such as that of Manila a substantial number of cases occurs in young age groups. Around 1990, 10% of all cases were 35-

39 years old[18]. The area includes 12 municipalities (Figure 1) each having municipal health centres in the township area and barangay health stations in more rural areas. In 1990, the estimated size of the female population aged 35-64 was about 340,000. The units of randomisation were 202 health centres (HCs) within the selected municipalities.

Randomisation *[Statement of Work: year 1].*. In 1995 the Department of Health (DOH) provided information on the size and level of deprivation (2 levels and missing) of the population resident in each of the 202 HCs. These were grouped by deprivation index and size and, within each group, randomly assigned to intervention or control arm. The deprivation index is updated at census surveys and reflects the presence and extent of squatters settlements in each HC.

Identification of the eligible population *[Statement of Work: year 1].* Nominative lists of women resident in the 12 municipalities and who were included in the electoral rolls were obtained from DOH. Women were identified by family and first name, date of birth, complete address (street and administrative area called barangay, which generally coincided with the area served by a health centre).

Intervention *[Statement of Work: years 1-3]:* . During 1995 a coordinating centre was set up. Nurses and midwives were recruited and trained in the technique of CBE using the MAMACARE ™ [20] programme already developed and tested in the Philippines, that makes use of silicone models of the breast for training purposes[21] and have been shown to enhance performance of examiners in previous studies[40,41,42]. Training was repeated for selected groups of examiners who missed 20% of the lumps or over-reported the number of lumps detected by more than 20%.
The first round of screening took place in 1995-1997 (30 months) and included 151,168 women ***[Statement of Work: October year 1 through December year 3].***
Eligible women resident in the intervention HCs were contacted in two ways: at the HC among those women who were attending for a variety of reasons, and, for those who did not, by systematic home visits. The nature and purpose of the trial were explained, and women were asked to give a signed assent to participation. They were interviewed, and CBE was carried out by the trained examiners. The interview addressed socio-demographic variables and classical risk factors for breast cancer. Scope of the interview was to assess baseline risk level to related this to the outcome of the intervention. Women were also instructed in the technique of breast self-examination (BSE) and provided with a leaflet in the local language explaining the purpose and methodology of BSE. Demographic characteristics of women who refused CBE were also recorded.

Women in whom abnormalities were detected were referred for diagnosis to special clinics that had been established in 3 major hospitals, and staffed by project personnel. The costs of transport to the clinic and of all medical procedures required to reach diagnosis were covered by the project. In addition, in the last year of the intervention period, a mobile team, comprising a doctor and a nurse and equipped to perform needle biopsies, carried out home visits for all positive women who had not reported to the referral centre, in order to obtain a final diagnosis. The diagnostic standard process consisted in a physical examination by a specialist doctors followed by biopsy if indicated. Mammography was not available even as a diagnostic modality.
Women in the control area received no active intervention, but were exposed to the general health education campaigns carried out by municipal authorities and voluntary bodies.

Interview of a sample of women resident in control areas*. [Revised Statement of Work: year 1]* In order to estimate the actual proportion of the control cohort that was present in 1999, and to compare the characteristics of this cohort with those of the intervention group a sample of women listed in the control electoral rolls was interviewed by means of the same questionnaire used in the intervention areas. This activity ceased when 1,000 interviews had been collected.

Follow-up *[Revised Statement of Work: years 1-5].* The aim of the follow-up of the intervention and control cohorts was to identify women who developed breast cancer and/or other cancers, those who died from other causes and those who migrated outside the study area.

The study populations were covered by two cancer registries, Manila-PCS and Rizal-DOH[19] that together serve the whole metropolitan area and the surrounding rural province of Rizal (Fig.1). The case-finding procedures of both registries were enhanced, so that they took place in a more timely manner than previously. Additional staff was recruited and trained to trace cases and report data by means of new abstract forms which included detailed information on extent of disease, tumour size, spread and nodal involvement. All registered cases of breast cancer were followed-up in 2001 to assess their vital status. Hospital records were first reviewed. Treating doctors and the cases' families were contacted for complement of information.
Project staff periodically visited the vital statistics offices of the 12 municipalities involved in the study to abstract information on all reported deaths, according to a standard notification form. The data were computerized and checked at the project office. The first follow-up phase (studying cancer incidence and mortality in the 2 years after the intervention) was completed in early 2002.

The staff of the cancer registries who performed the follow-up was blind with respect to which cohort a case belonged.

Cases of breast cancer, and deaths from breast cancer, identified during the follow-up period were linked with the master file (interviews and CBE results) and lists of eligible populations (intervention and control areas) using a probabilistic record linkage software 'RECLINK'[1]. Records matched are distinguished in three groups depending on the value of the matching score: 1) definite match 2) possible match but requiring manual verification 3) non-match. Records in group 2) were verified using paper documents and a decision made (DE).

Data analysis ***[Revised statement of Work: years 6-8]***. The principal outcome measure is the number and cumulative incidence (CUMI) of breast cancers in the intervention and control cohorts. Sensitivity, specificity and predictive value have been calculated using diagnosis of clinical cancer due to the test, or in two years follow-up, as the criterion of "true positive", since only one screening round was performed. Additional parameters describing the performance of the intervention are presented as absolute and relative frequencies, means and their standard deviations and 95% confidence limits (c.l.). Comparisons are univariate or age-adjusted as indicated. Because of the huge numbers of subjects involved, statistical testing would not be informative and has been avoided when comparing cohorts. Confidence limits of proportions are based on the exact binomial distribution.

[1] RECLINK is a record linkage software developed at unit of Descriptive Epidemiology, International Agency for Research on Cancer, Lyon. The software performs probabilistic linkage between records from different sources using selected personal identifiers (names, date of birth, sex, address, tribe).

Results

Randomization. There were 101 HCs in each arm (intervention and control). The overall estimated number of people resident in the two arms was very similar, 1.82 million, as was the estimated proportion of deprived population, 29.2% in control areas and 28.8% in the intervention areas.

Nominative lists of the population. We compared counts and age distributions of the population by study arm and municipality based on the census data, nominative lists generated from electoral rolls and the questionnaires of interviewed women. Overall the three sources gave similar counts with differences between any two in any one municipality that were less than 5%. The two exceptions were Pasig and Las Piñas in which census data estimate 6% more population. Distributions by age were also similar (details not shown).

Intervention. The results of the intervention after completion of the single round of examinations, and the newly diagnosed breast cancer cases in 2 years of follow-up are summarized in Table 1. The number of women interviewed and offered CBE was 151168; compliance with examination was 92% (138,392). Three thousand four hundred and eighty-three women (2.4% of those examined) were judged to have a lump at the first examination by the nurses and were referred to the project clinics. Of these, 1293 (37.1%) received further investigation, and complete diagnostic follow-up was achieved for 1220 women (35% of those positive on screening).

1478 women (42.5%) actively refused further investigation, even with a home visit, and 785 (22.5%) were not traced, and were either reported by the neighbours or assumed to have moved away or died.

Among the 1220 women with complete follow-up 34 malignant cancers were detected; the presence of a lump was not confirmed in 563 (46.1%) and 623 (51.1%) were diagnosed as having benign breast disease.

Because of the poor compliance with follow-up of screen positive women, even with home visits, the active intervention was discontinued after completion of the first screening round in December 1997.

During the two years following the end of the intervention, 4 cases occurred among complying women initially diagnosed with benign disease (CUMI=3.4/1,000); 9 cases were identified among refusers (CUMI=6.1/1,000) and 10 in women not traced at follow-up (CUMI=12.7/1,000)(table 1).

Interview of women living in control areas. The nurses sought sequentially 1,624 women of a list of names randomly extracted from the electoral rolls of control areas. Sixty-two percent of them (1,011 women) were located, of these 999 (99%) were interviewed. Of those not located 12 (0.7%) had died; according to neighbours 296 (18% of all) had moved away the remainder were unknown to residents at given address.

Comparison of characteristics of examined, refusers and control women.

Table 2 shows some socio-demographic characteristics of the three groups as assessed at interview, women in intervention areas interviewed and examined, women interviewed who refused CBE and the sample of women resident in control areas. The three groups were very similar in age, 44.8±8.2 years, 44.7±8.4 and 44.0 $\pm$ 8.1 respectively, and were also of similar age at menarche, between 13.0 and 13.6 years. The three groups differed for other variables. Refusers were one year older than compliers at their first full-term pregnancy; controls were slightly younger. Conversely, refusers were of higher socio-economical level than compliers as shown by the proportion of women who attended college (18% *vs.* 12%), had a significantly greater income (medians were Pesos 7,000/month *vs* 4,500), were more often nulliparous (17% *vs*. 10%) and less likely to have had 5 or more children (25% *vs.* 33%). Women interviewed in the control group were similar to refusers with respect to being of relatively high educational level (19% attended college). However, this sample declared a much lower income than the other two groups, a significant lower proportion was nulliparous (3%) and a lower proportion had had 5 or more children (21%). Thirteen percent of compliers stated that they were using oral contraceptives and 21% reported other contraceptive methods. The corresponding percentages were 9% and 13% among refusers and 6% and 9% among controls. Around 70% of the women in all groups had never had a cervical cytology test. Tobacco smoking is a rare habit in this population, 8% of compliers were regular smokers, 7% of refusers and 5% of control women. Eight percent of examined women regularly drank alcoholic beverages. The proportion was 11% among refusers but much higher among controls, 26%.

Comment on implications in discussion

Rate of positive women by selected personal characteristics.

Among examined women the referral rate decreased constantly with age from 2.9% in women below 40 to 1.5% in women aged 60 or more (table 3). More women were detected positive among those with less than three pregnancies (3.3% *vs.* 2.2%) and among those who attended cervical screening (3.3% *vs.* 2.1%). The detection rate was not consistently associated with the level of education and was higher in women with lower income. The detection rate ranged from 1.1% to 6.0% in the 12 municipalities. Rates above the average were recorded in the more affluent areas of Makati (4.0%), Mandaluyong (6.0%) and Malabon (3.9%).

Record linkage between Master Files (MFs) of women interviewed and lists of the eligible population.

The master files (MF) of the women interviewed were matched with the lists of the eligible populations, intervention and control cohorts, with the files of newly diagnosed cases and with death certificates. Only 19% of the women interviewed and examined in the intervention cohort were linked with records of women in the electoral rolls. The proportion of records matched varied significantly by municipality, 7% - 36%. In running the linkage procedure we adopted a conservative attitude maintaining only matches that scored at least 95%. The discrepancy reflects the high turnover of the resident population. The electoral rolls released for the study had not been updated since the previous political elections. Assuming that the same bias affects electoral rolls of the two randomised arms, these denominators would be suitable only for the comparison of the incidence in the intervention arm relative to the control one.

Follow-up.

Information of persons dying and for whom cancer was recorded on the death certificate is part of the routine case-finding procedure for both cancer registries. Abstraction of information from death certificates at the vital statistics offices of the 12 municipalities was carried out at regular intervals as part of the enhanced case-finding referred to above. However, it became apparent that information from this source would be inadequate as a method of evaluating breast cancer mortality. Substantial omissions were evident, and the distribution of causes of death among records encoded in the first 6 months showed significant biases with cancer being over-represented. Here we report on the cumulative incidence of new cases that were included by the two cancer registries covering the municipalities where the project cohorts were recruited. Since we do not know the exact person-years of observation, rates were calculated as the number of new cases identified by 31 December 1999 in a cohort, divided by its size at recruitment. Date of

recruitment of women in the control arm (that are known only through electoral rolls) was set to the mid-point of the recruitment period that is 1 December 1996.

Overall 518 breast cancer cases, incident in 1995-1999, were linked with records of women in the electoral rolls or in the intervention cohort, after exclusion of cases whose incidence date preceded date of recruitment. Figure 2 illustrates how they were partitioned by cohort, together with the cohort size. The CUMI of breast cancer was 11.6/10,000 women in the control arm, 9.7/10,000 in the intervention arm as identified by electoral rolls and 9.1/10,000 in the women invited for screening (interviewed cohort). All of the 137 cases identified among interviewed women had complied with CBE. Eighty of these had been judged negative on CBE (table 4) corresponding to a CUMI of 5.9 new cases per 10,000 women. Fifty-seven cases were detected among the 3,483 women who were screen-positive, 38 of which were diagnosed through the intervention itself (CUMI 2.7/10,000) although 4 were among women initially diagnosed with benign disease (table 4). Nineteen cases occurred among those women who did not complete the diagnostic process (CUMI 84.0/10,000). Table 4 also gives the cumulative incidence of BC by time since CBE. Thirty out of 38 screen-positive cases were diagnosed within 12 months of the first examination, only 4 were diagnosed later. All of the four malignant BC that occurred in women who were considered to have benign disease were diagnosed more than 12 months later. Of the 19 cases identified among refusers 11 occurred within a year and 8 later. The 80 cases diagnosed among screen-negative women were almost equally distributed between the two periods.

Test sensitivity. If we generously allow that every positive examination in a woman who eventually proved to have cancer (within 2 years of the test) is a true positive, then the sensitivity was 41.6% (57/137), the specificity 97.5% (134829/138255), and the positive predictive value 1.6% (57/3483). However, only 34 cases were actually diagnosed through the intervention reducing sensitivity to 24.8% and positive predictive value 1.0% (34/3483).

Table 5 shows the clinical extent of disease as recorded in the cancer registry database for the 34 cases who were correctly diagnosed as having cancer by the screening process, compared with the cases occurring in the women who were screened negative (80), who did not attend the diagnostic follow-up (19), or who were evaluated as having only benign disease when they did (4). None of the screen-detected cases had distant metastasis at presentation while 19.8% (95% c.i. 12%-30%) of the screen-negative group had metastatic disease. However, cases with localized disease were more common among screen-negatives, 20% *vs.* 11%. None of these differences were statistically significant.

Figure 3 shows the distribution and 95% c.i. by stage at presentation of the cases identified in the two arms (intervention and control) as defined by electoral rolls. The information was not available for 16% of the cases in both groups. Thirty-six percent of the cases were localized in the intervention group compared with 31% in controls, all at the expense of regional involvement the frequency of which was 49.7% (95% c.l. 42.1-57.3) and 53.8% (95% c.l. 46.3-61.2) respectively (not statistically significant). Fifteen percent of the cases presented with distant metastasis in both groups.

Survival of breast cancer cases

In 2005 we completed the analyses of survival time after diagnosis of the cases detected in the study. The proportion of inadequate fine needle biopsies in the project tumour clinics was 26% a figure well compatible with Western standards. The median survival time of screened-detected cases who complied with treatment was 13.4 months, significantly greater than median survivals of refusers (6.0 months) and self-reported cases diagnosed in the control areas (3.9 months).

Discussion

Breast cancer is an increasing problem in developing countries. Increases in incidence and mortality are widespread, often more marked in younger generations of women[22]. Several reports indicate increases between 1% and 3.6% in populations of South-Eastern Asia[23,24,25,26]. Known risk factors are linked to reproductive history and lifestyle and are hardly modifiable, rather they are likely to become more prevalent with economic development. In these circumstances, interest has tended to focus upon early diagnosis and treatment as a means of reducing at least mortality. The screening method that has been proved to be effective in is mammography that can reduce breast cancer mortality by 25% in women 50-69 years of age[8]. However, a screening programme that requires examination of all women aged 50-69 at least every 2 years, by specialist radiologists, would pose impossible financial and logistical burdens on most developing countries. Moreover, the impact would be relatively small, too; in the area covered by the two Filipino cancer registries, only 40% of breast cancer cases occur between the ages of 50 and 69[18,19], so that the potential reduction in breast cancer mortality even with a well-implemented screening programme would be only about 10%.

The efficacy of breast self-examination as been formally tested in a randomised trial in Shanghai, China[13]. No significant reduction of breast cancer mortality in the intervention group was detected after 10 years of follow-up and the distributions of stage at diagnosis in screen and control groups

were very similar. However, the small size of the lesions diagnosed in the control subjects in this trial (47 % ≤2 cm diameter, 48% node negative) suggests a high level of health-awareness in this special subset of the Shanghai population, and may give little scope for improvement in outcome through early detection by BSE.

Clinical Breast Examination carried out by a trained examiner has many attractions. In programmes where it is combined with mammography, CBE finds fewer lesions but does detect some that had been missed by mammography. In general the differential is less for younger women[29]. In the CNBSS II trial of women ages 50-59, there was no significant difference in the efficacy of CBE and mammography[17]. CBE has been introduced as a single screening modality in Japan. There is some suggestion that, where coverage by such screening is high, breast cancer mortality rates have declined more than in other areas[30], although a case-control study was inconclusive[31]. Manpower requirements for a screening programme based on CBE would be expensive but in many developing countries these are generally easier to mobilize, than the technology required for mammography. Based on these arguments, it has even been suggested that CBE would be a more cost-effective alternative to screening women at high risk, in low-income countries[32].

The trial in the Manila area of the Philippines was designed to assess whether a meaningful reduction in mortality from breast cancer could be achieved in a developing country, using only screening by physical examination of the breast performed by trained health personnel, nurses and midwives. The mortality reduction that was aimed for, among the women actually screened and followed-up, was 25%, that is a smaller effect than that of mammography which had been demonstrated in RCT settings to reduce mortality by about 30-35% among screened women, and probably the minimum mortality reduction that would be worthwhile in any future programme. The Manila area was selected for the trial for several reasons, most important the relatively high incidence of breast cancer as high as in Southern Europe; the availability of treatment facilities (surgery, radiotherapy and systemic therapy are provided by both the public and private sectors), and a large number of well-qualified nurses could be recruited to act as examiners. Even with this high incidence, realistic assumptions about survival -two thirds the stage-specific survival reported by the SEER programme in the USA around 1980[33], and the observed stage distribution in Manila - and sub-optimal compliance (70%), the study had to be large – 166,000 in each group (intervention and control) to have a 75% chance of finding a significant difference ($p<0.05$) after 6 years follow-up[34]. In settings with lower incidence rates, as in the majority of developing countries, a meaningful trial is virtually impossible.

The unexpected result that jeopardised the whole intervention was the unforeseen reticence of women found with abnormalities and informed of the implications to their life, to pursue diagnosis and treatment. This problem had, in fact, been noted during a pilot phase for the main study. Logistic (distance/inconvenience) and financial barriers were identified as the main determinants to non-attendance at the follow-up clinics. In the main study, these problems were addressed from the beginning by provision of free transport and consultation. As the study progressed, it became apparent that this tactic was not sufficient, and a programme of diagnostic home visits was introduced. Even this failed to raise compliance with diagnostic follow-up beyond 35%. Understanding the deep reasons of such negative attitude will require *ad hoc* studies involving the collaboration of epidemiologists, sociologists and psychologists.

The second major limitation highlighted by this study is the modest sensitivity of the screening test in that context. This result at least reflects what might realistically be expected from CBE as a screening modality, applied by nursing personnel, in a developing country where infrastructures for cancer diagnosis and management are necessarily even more limited than for other diseases of greater burden. The examiners were all nurses and received formal training from medical personnel who themselves had considerable experience in CBE. Nurses with apparently aberrant detection rates (high or low) attended additional training sessions (the evaluation of this phase was carried out by CN but not formalised through recorded results and quantitative evaluations). Clearly, if CBE is to be at all useful, a much greater effort in training and quality control of performance than was possible in the Manila trial will be required. This may be an unrealistic expectation if it is to be applied as a mass screening method in a service setting.

Sensitivity and specificity are not directly comparable with measures from other studies or programmes since the definition of the reference true cases varies. Nevertheless, sensitivity and specificity of BCE was substantially higher in other studies where either similar[35,37,38,39] or more sensitive definitions for the gold standard were used[36].

Our study have also highlighted additional problems, relevant in the planning of future interventions, that normally are key aspects in the evaluation of randomised trials but were made unimportant given the low compliance with referral. They include the feasibility of long-term follow-up due to high mobility of the population, the lack of up-to-date registers of the resident population and the inefficiency of block randomisation.

More dramatic is the observation of the failure of 2/3 of the women who were judged abnormal on their screening examination, to attend for follow-up and treatment. All the women taking part in the study had had the objectives and possible outcomes of screening explained to them, and had given their informed consent. Compliance with the first examination was very high (92% of those approached). Most studies of the factors influencing attendance for breast cancer screening have concentrated on characteristics associated with participation with the screening examinations[8]. In general in Western countries more affluent, better educated and younger women are more likely to attend. In contrast, in the very different cultural milieu of Manila, the women refusing to participate were generally of higher socio-economic status. The same observation was made in relation to a community screening trial for cervix cancer in rural India[43]. We speculate that in developing countries affluent people normally using private medical care refuse offers from the public service that perceive to be of low quality. In affluent countries contacts with medical services are frequent and access to information and services is generally good. Demand is high and often translates in over-medication. Conversely, in developing countries, expectation in the general population is low with respect to both efficiency and efficacy, which may explain low compliance with clinical follow-up.

COMPLEMENTARY STUDIES

Analysis of risk factors for breast cancer in the female population of Manila

The file of the breast cancer case register have been linked with the file of the intervention cohort and led to the identification of 169 cases. By comparing the date of diagnosis of cancer with the date when the participant was interviewed we identified 46 prevalent cases that were excluded from subsequent analyses. For each of the remaining 123 cases, eight controls were randomly selected from among all women in the cohort having the same age ($\pm$ 2 years), date of interview and PE ($\pm$ 4 months) and municipality of residence. Vital status of cases and controls is being assessed. Those traced and alive will be re-interviewed, proxies will be approached otherwise. In addition to assess vital status the scope is to update the information on reproductive factors that may well have changed since first recruitment, in this population characterized by high fertility.

We have conducted an analysis of the association between socio-demographic and reproductive variables and the risk of breast cancer, based on interviews collected at recruitment. The association between the factors analyzed and the risk of developing breast cancer is expressed by the relative risk (RR) estimated by conditional logistic regression for matched data. Ninety-five

percent confidence limits (95% CI) express statistical significance of the RRs. The results are shown in Table 6.

There is no association between breast cancer and socio-economic level expressed by the average income per family member. On the contrary we observe a strong association with fertility: the incidence of breast cancer is 3 times greater in women with no children compared with women with 6 or more full-time pregnancies (RR=3.3, 95%cl 1.6-6.7). Their risk is even greater when compared with women who had their first child before age 19 (RR=4.8, 95%cl 1.8-13.2). We also observe clear dose-response relationships between parity and age at first child.
These results are in agreement with the literature but the associations reported are unusually strong.

TREATMENT PRACTICES FOR BREAST CANCER IN MANILA

Around 1995 the incidence of breast cancer in the female population of Manila was 57.4/100,000 (world standardised), the highest in Asia excluding Israel and even higher than in some areas of Southern Europe. Since early breast cancer can be treated effectively we conducted a descriptive study of the treatment regiments that are provided

Source data were obtained from the data set of the PCS-Manila Cancer Registry. Breast cancer cases incident in 1991, 1994 and 1997 were selected. After exclusion of cases recorded on the basis of the death certificate only, and of those registered as metastatic at diagnosis (summary stage routinely recorded by the registry), we drew a random sample of 992 cases. An abstract form was prepared to collect information on diagnostic procedures, TNM stage, and treatments received separated into surgery, radiotherapy, adjuvant chemo and hormonal therapy. Dates of first administration and the names of the treating doctors were also abstracted. Medical records of all the cases were reviewed first. Treating doctors were then contacted by one of the authors (AL) to obtain complementary information, particulary on the use of adjuvant therapies that are often administered in private practices.

The 992 cases were almost equally distributed in the three incident years of interest (301, 342 and 349 respectively). Forty cases were advanced at diagnosis and therefore excluded, and no clinical information could be traced for 207 (21%) leaving a total of 745 cases, of whom 98% were microscopically verified.

Staging. 99% of the cases received a chest x-ray and less than 4% were also examined by computerised tomography, liver ultrasound or bone scan. Stage was not assessed for 5% of the cases. Ten percent were stage I; 31%, IIA; 29%, IIB; 26% stage III. This pattern was constant in the three years considered.

Treatment. 97% of the cases received radical mastectomy irrespective of stage at presentation. Only 17% of the cases received radiotherapy and the proportion increased steadly from 8% in stage I to 27% in stage IIIB. On average 53% received adjuvant chemotherapy; the proportion treated was higher in women below 50 years of age (55%) and declined to 35% in cases aged 60 or more. There was not a systematic association with stage at presentation.

Finally, tamoxifen treatment was administered to 51% of the cases with a significant inverse association with age (57% of cases below 50 years were treated *vs.* 42% in age group 60+ years). We also observed a trend towards an increasing proportion of treated cases with stage becoming more serious: 39% of stage I *vs.*58% in stage 3B. The use of hormonal treatment almost doubled between 1991 and 1994 and remained stable thereafter.

We have shown in previous studies that still too many cases of breast cancer present at diagnosis with advanced disease. With this work we show that standard treatment for non-metastatic cases is sub-optimal. In a country with limited resources interventions to improve and generalise access to optimal treatment for tumours that are potentially curable, would be cost-effective and should be high priority.

PREVALENCE OF RISK FACTORS FOR CHRONIC DISEASES IN THE FEMALE POPULATION OF MANILA

Table 7 shows the distributions of Body Mass Index (BMI), blood pressure and consumption of alcohol and tobacco in a sample of 1300 women resident in Pateros, one of the municipalities included in the intervention, in 2005.

Alcohol drinking and tobacco smoking remain a rare habit among women. However, 49% of this relatively young population is overweight, 10% is obese.

Table 1.
Results of the single round of screening, and clinical outcome after 2 years of follow-up.

Number of women interviewed:	151,168	
Number of women examined:	138,392	(91.5%)
Number positive on screening:	3,483	(2.4%)

Women CBE-positive		Cancers diagnosed by screening	Cases after 2 years of follow-up
1,220	Completed diagnostic follow-up	34	38
556	at project clinics	21	
73	at another clinic	1	
590	at project clinic after home visit	12	
1,478	Refused or follow-up incomplete		9
785	not traced		10
3,483	Total		57

Cancer detection rate per 1,000 examinations:

Total cancers found in women screen-positive:
57/ 3,483 = 16.4 /1,000

Cancers actually detected by the screening programme:
34/ 3,483 = 9.8 /1,000

Table 2.
Comparison of characteristics of interviewed women who refused examination, those who accepted and a sample of women living in control areas.

	compliers N=138,392	refusers N=12,776	control sample N=999
age in years (mean±SD)	44.8 ± 8.2	44.7 ± 8.4	44.0 ± 8.1
attended college/university (%)	12.3	17.7	18.6
monthly income (pesos)			
mean±SD	5744 ± 5590	10806 ± 12023	2786 ± 2908
median	4500	7000	1000
Income/No. of cohabitants	1556 ± 1713	2748 ± 3292	511 ± 608
mean age at menarche	13.6 ± 1.7	13.4 ± 1.5	13.0 ± 1.4
mean age at first fullterm	23.0 ± 4.5	24.1 ± 4.5	22.6 ± 3.8
ever used oral contraceptives	13.3	8.9	6.0
ever used any contraceptive	20.8	13.1	9.4
nulliparous (%)	10.3	16.6	2.7
women with 5 or more children	32.6	25.3	21.5
never had a PAP smear (%)	69.9	72.3	73.3
smokers (%)	7.7	6.5	5.1
drinkers (%)	7.8	11.2	26.2

Table 3.
Percent rate of positive women by selected personal characteristics.

		No. positive	No. examined	positivity rate %
		3,483	138,392	
age	< 40	1,356	46,896	2.9
	40-49	1,443	53,459	2.7
	50-59	538	28,470	1.9
	60+	145	9,543	1.5
	unknown	1	24	4.2
education	max prim	925	59,803	1.5
	max secon	997	50,221	2.0
	college+	312	17,072	1.8
	unknown	1,249	11,296	11.1
pap-test	ever	1,290	39,285	3.3
	never	2,017	96,789	2.1
	don't know	176	2,318	7.6
Full-term	<3	1,302	39,777	3.3
pregnancies	3+	1,920	87,562	2.2
	missing	261	11,053	2.4
Monthly income	low	1,679	60,799	2.8
per No. of cohabitants	high	1,031	57,998	1.8
	unknown	674	19,595	3.4

Table 4.
Breast cancer cases (BC) identified in the intervention cohort after 2 years of follow-up, by screening outcome and time since PE.

	Number of women	No. incident BC in first 12 months	No. incident BC in more than 12 months	No. incident BC all	No. of cases per 10,000 examined
Screen-negatives, all	*134,909*	*36*	*44*	*80*	*5.9*
Screen-positives, all	*3,483*	*41*	*16*	*57*	*163.7*
Screen-positives by screening outcome:					
Refusers and lost	2,263	11	8	19	84.0
Compliers:	1,220	30	8	38	311.5
Malignant breast cancer	34	30	4	34	
No mass or benign breast disease	1,186	-	4	4	33.7

Table 5.
Breast cancer cases that occurred among screened women, by stage at diagnosis and screening outcome. Numbers, percentages and 95% c.l.

	unknown	Localised	Regional	Distant	Total known stage
Screen-detected					
No (%)	14 (42.4)	2 (10.5)	17 (89.5)	0 (0%)	19
95% c.l.	*25.5 – 60.8*	*1.3 – 33.1*	*66.9 – 98.7*	*0 – 17.6*[*]	
Screen-negative or Screen-positive lost to follow-up or screen-positive benign disease	18 (17.3%)	17 (19.8%)	52 (60.5%)	17 (19.8%)	86
95% c.l.	*10.6 – 26.0*	*12.0 – 29.8*	*49.3 – 70.8*	*12.0 – 29.8*	
Total	32 (23.4%)	19 (18.1%)	69 (65.7%)	17 (16.2%)	105
95% c.l.	*16.6 – 31.3*	*11.3 – 26.8*	*55.8 – 74.7*	*9.7 – 24.7*	

[*] one-sided 97.5% c.l.

Table 6. Numbers of cases and controls, odds ratios (RR) and 95% confidence limits by levels of risk factors.

Factor	No. cases	No. controls	RR-a	95% c.l.
Family income (*):				
<667 §	25	223	1.	
667-	26	185	1.3	0.7-2.3
1167-	22	190	1.0	0.6-2.0
1875+	28	205	1.2	0.6-2.4
Unknwon	22	176	1.1	0.6-2.1
Age at menarche (years):				
<12	11	71	1.3	0.6-2.8
12-	27	182	1.3	0.7-2.2
13-	52	438	1.0	0.6-1.7
15+ §	32	276	1.	
Unknwon	1	11	0.8	0.1-6.3
No. of full-term pregnancies:				
Nulliparous	25	115	3.3	1.6-6.7
1-2	30	161	2.7	1.4-5.4
3	16	161	1.4	0.7-3.1
4-5	23	244	1.3	0.6-2.6
6+ §	14	193	1.	
unknown	15	104	2.2	0.9-5.0
Age at first pregnancy (years):				
<19 §	79	420	1.	
19-21	5	105	1.5	0.5-4.5
21-24	10	141	2.1	0.8-5.7
25+	22	220	3.7	1.5-9.6
nulliparous	25	115	4.8	1.8-13.2
unknown	7	92	0.9	0.2-3.9
Age at menopause (years):				
<45§	6	64	1.	
45-47	12	65	2.0	0.7-5.6
48-50	5	61	1.0	0.3-3.4
50+	18	97	2.3	0.8-6.3
Premenopausal & unknown	82	691	1.1	0.5-2.8

(*) Average annual income per family cohabitant in Pesos.
§ Reference category for the OR.
RR-a: RRs adjusted for age and residential area.
RR-b: RRs adjusted for age and residential area and mutually adjusted for each other.

Table 7.
Prevalence of risk factors for chronic diseases in Pateros, Metro Manila November 2005

	All.	%
Age (yrs)	1318	
<49		55.9
[49-69]		35.1
>69		9.0
BMI (kg/m2)	1010	
<18.5		8.0
[18.5-24.9]		48.9
[25.0-29.9]		32.8
>29.9		10.3
Blood pressure (mmHg)	1094	
<10/6		11.1
[10/6-14/9]		76.9
>14/9		12.0
Regular smokers of tobacco cigarettes	1318	12.0
Regular consumption of alcoholic beverages	1318	7.4
Sedentary life-style	1318	9.6

Figure 1.
Municipalities of Metro Manila and Rizal Province included in the study and covered by two population-based cancer registries.

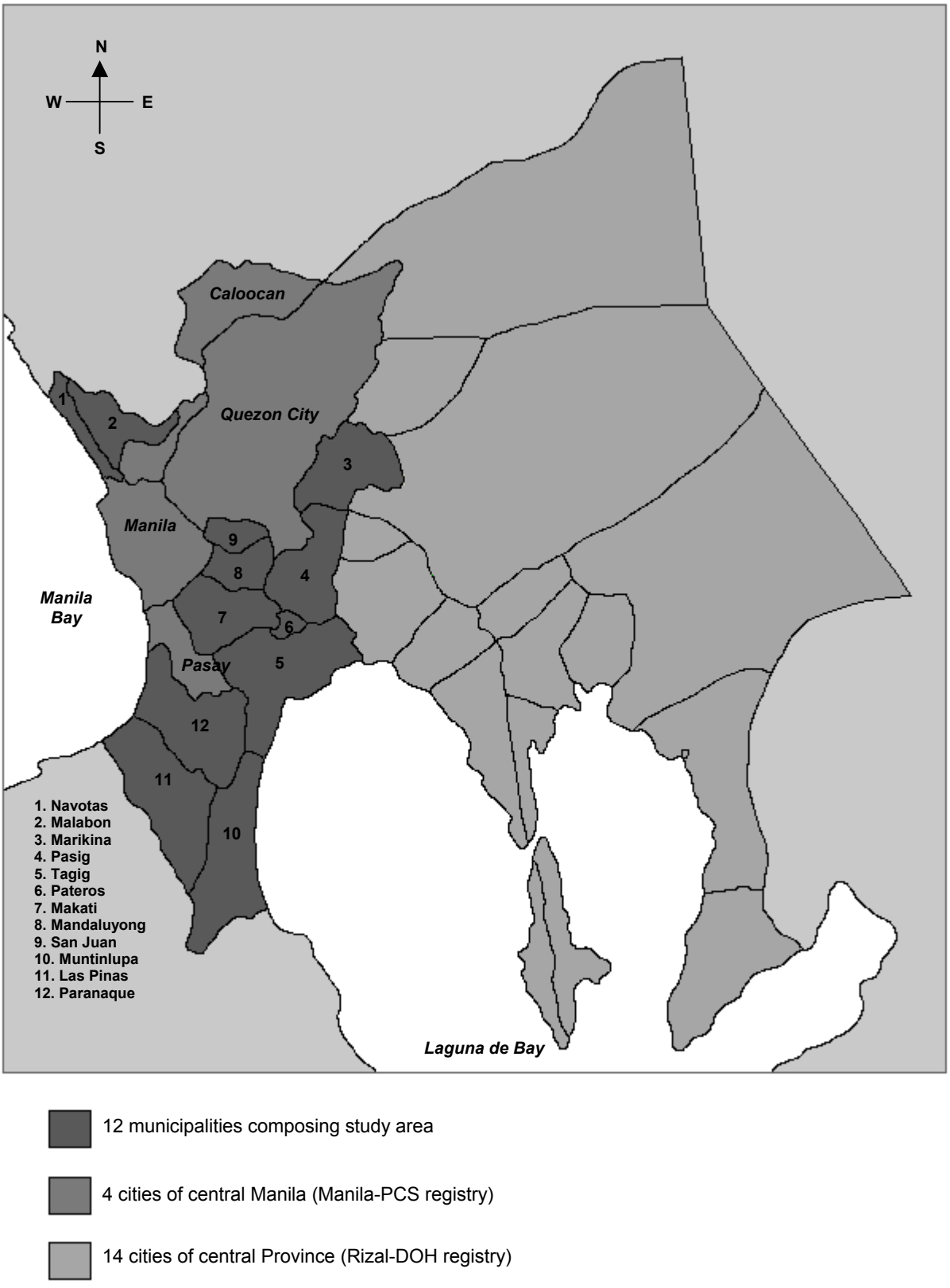


Figure 2. Follow-up to 1999 – New cases of breast cancer identified in control (218) and intervention (211) arms as defined by electoral rolls. Of the new cases in the interviewed cohort (137), 48 were also linked with records in the electoral rolls. In brackets number screen-detected cases. In parentheses italics cohort size.

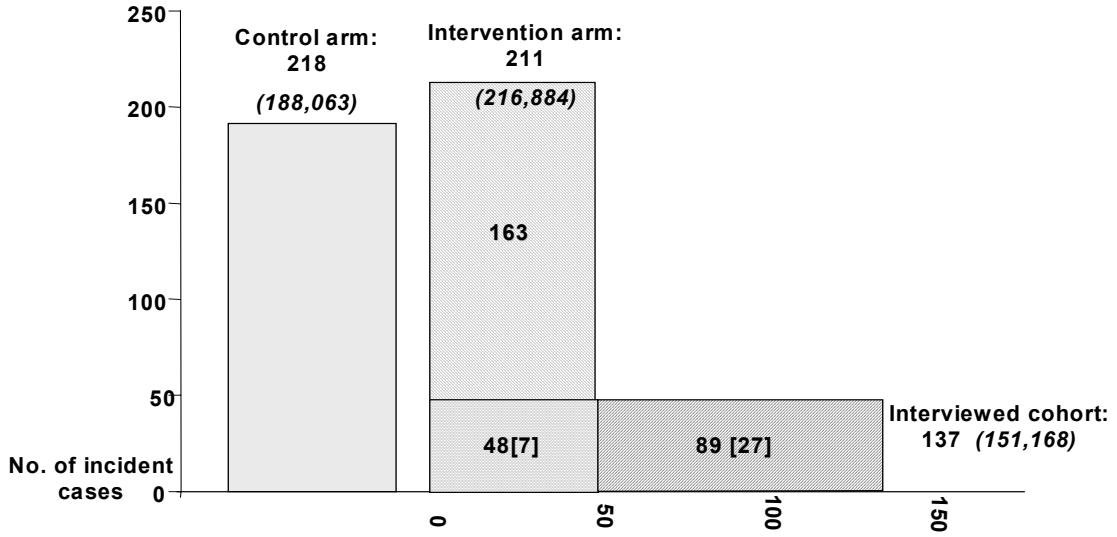
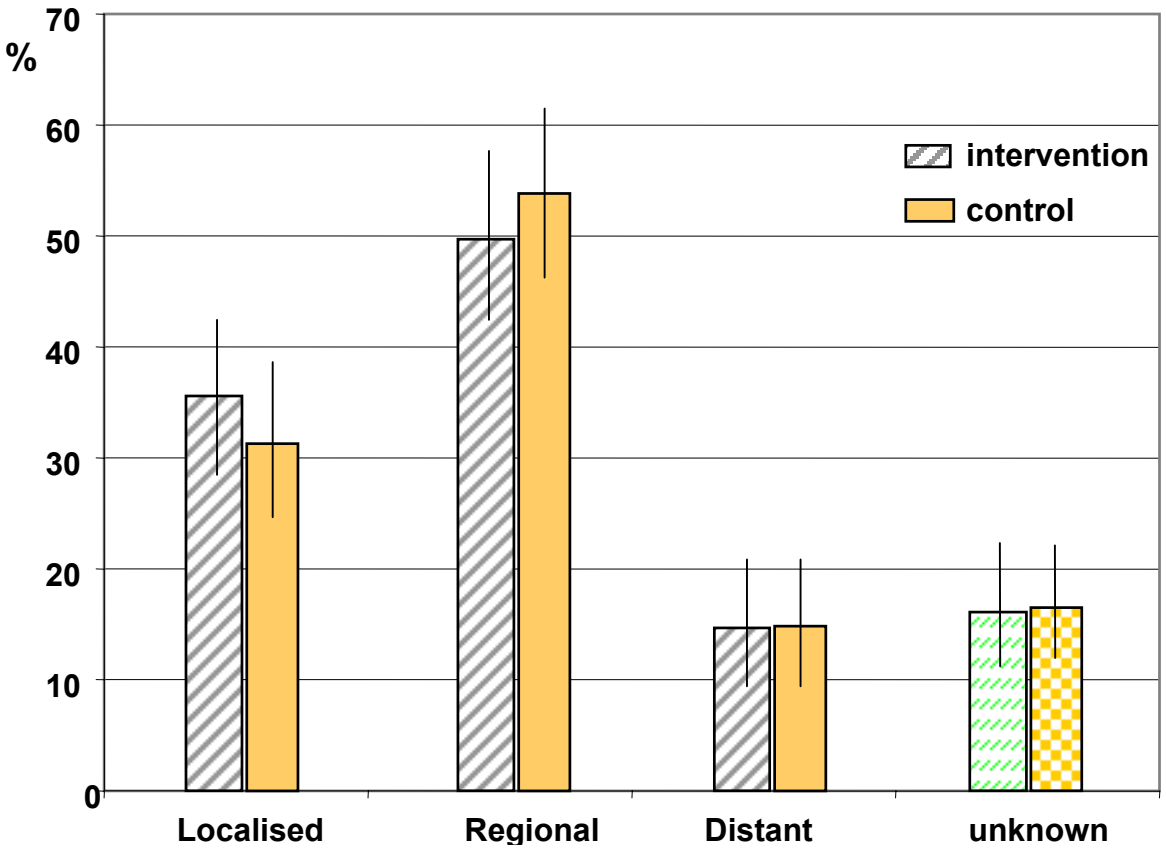


Figure 3. Incident cases by stage in the two arms defined by electoral rolls.
Percent and 95% c.l. of 211 and 218 cases in intervention and control arm respectively.



KEY RESEARCH ACCOMPLISHMENTS

- Quality of breast cancer treatment and care in a developing country.
- Risk of breast cancer in relation to several characteristics of women's reproductive life, obesity, height, alcohol consumption, family history of breast cancer and tobacco smoking.
- Prevalence of risk factors for breast cancer in the female population of Metro Manila.
- The same factors above plus education and socio-economical level as determinants of stage at diagnosis of breast cancer and survival, taking account of treatment received.
- Determinants of compliance with early diagnosis and treatment in a developing country.

REPORTABLE OUTCOMES

- Poster presentation at the Era of Hope Conference, Washington D.C., 1-4 October 1997.
- Poster presentation at the Era of Hope Conference, Atlanta, 8-11 June 2000.
- Poster presentation at the second Era of Hope Conference, Orlando, 25-28 September 2002
- REC-LINK software program – for automatic matching of records based on personal id-items (e.g. name, surname, age, date of birth, address).
- Database of the female population resident in Metro Manila in years 1995-1996.
- Database of new cancer cases diagnosed in the resident population 1990-2001.
- Database of incident breast cancer cases, years 1995-2001, with clinical details of stage at diagnosis and initial treatment.

Conclusion

Although logically attractive, an organized screening programme based on BCE undertaken by health workers is likely to be very difficult to implement in practice. Our study shows that a one-time contact with unknown health workers has a minimal impact on the attitude of this population towards early diagnosis. Yet, early diagnosis remains the top priority in order to improve the lamentable stage distribution observed in most developing countries. An alternative option to be investigated is to promote the early detection of BC among health operators in first level primary care services, those that interact with the population on a daily basis. In this context, there is value in teaching and encouraging BSE, and training health workers in opportunistic CBE to be performed in women presenting possible lumps and encouraging referral to specialist centres.

The seeming paradox of accepting the screening examination, but not its consequences (the follow-up examination) requires further investigation. Twenty-one percent of referred women who decided not to undergo investigation gave reasons not related to logistical or financial barriers. It is known that a patient's decision making is not always manifestly rational. Misinformation, denial, overconfidence, distrust and confusion may all play a role[54]. Apart from trying to clarify what were the important factors in the present instance, this outcome of the Manila trial is a reminder that it is not only the technical efficacy of the screening procedure that needs to be considered when introducing community screening in developing countries; specific culturally-related health-belief issues need also to be taken into account.

Nevertheless, the latest results on the survival on breast cancer patients detected in the study also showed that good quality management can be provided with affordable and sustainable investments, even in the context of limited resources, and that improved management can have a significant impact on clinical outcome. These results shows that a rational use of available resources may reduce mortality. A health system capable of improving survival and quality of life

will contribute to the credibility of awareness campaigns and help to change the negative attitude of the population.

A scientific report on the study is in press:
Pisani P, Parkin DM, Ngelangel C, *et al.* Outcome of screening by clinical examination of the reast in a trial in the Philippnes. (2006) Int J Cancer, 118:149-154

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APPENDICES

ANNEX 1 ***Proposal 1993***

STATEMENT OF WORK

Year 1

Update list of health centers (HCs), catchment zones and personnel eligible to participate as exarniners.

Allocate HC's to intervention and control groups.

Verify socio-demographic profile of intervention and control populations.

Training of designated HC personnel in PE, and in BSE techniques at 15 training seminars. Set up mechanisms for evaluation of performance by exarniners.

Establish recording and data entry systems.

Establish hospital clinics for referral of diagnosed cases, including patient transport and follow-up. Mechanisms for documentation of results.

Rizal cancer registry - train 2 new staff in active case-finding in hospitals, and recording size and stage of tumours. Set up procedures for active follow-up of breast cancer cases.

Establish population lists in entire study area.

Year 2

ln intervention areas perform PE and give BSE instruction to eligible women who agree to participate. Update population lists. Ensure reimbursement of women referred to hospital and follow-up of non-attenders.

Co-ordinating centre implements and updates documentation systems (enrollment, screening, follow-up, outcome) and commences data entry.

Year 3-6

Complete 2nd-5th screening rounds.

Refresher course in PE/BSE during year 3.

Co-ordinating centre updates documentation systems and continues data entry.

Evaluate - compliance and loss to follov-up at screening.
- compliance and results of hospital referral

Review performance of screening tests. Evaluation of probable sensitivity and specificity. Advise on improvement to methods.

Review cancer registry procedures, especially staging information and completeness of follow-up.

Estimate incidence of cancer and of advanced cancer, in intervention and contral groups.

Estimate mortality from breast cancer in intervention and control groups.

Years 7-8

Establish population lists in entire study area. Evaluation phase.

Complete analysis of results - intermediate endpoints and mortality in intervention and control groups.

Publication of results.

Proposed revision of Statement of Work

The budget remaining can cover remaining field activities (first 6 months of 1998) and the follow-up of the cohort for 6 years from 1998 to 2003. The main costs are due to search of information (hospitals, death certificates and direct contacts) and abstraction and reporting in a timely manner; maintenance of the data bases including automatic record linkage and manual handling of uncertain matches, coordination and periodic analyses. A detailed cost estimate is given in attached and reflects the following Statement of Work.

Year 1 - 1998

Complete data entry of forms relative to women examined during the first round of screening completed by December 1997.

Complete home visits (home biopsies) of women detected positive who do not attend referral clinics for final diagnosis.

Re-examine a random sample of 5,000 women screen-negative at first examination.

Interview a random sample of 1,000 women drawn from the population lists of the control areas.

Recruit and train cancer registry personnel to trace and abstract clinical information and vital status of breast cancer cases.

Set up procedures to update the file of breast cancer cases (enter new cases, record changes of address, record changes of vital status and related information), and match files of cases with those of the intervention and control cohorts and of death certificates.

Undertake routine activity of follow-up.

Perform periodical analyses of the data collected and report on current status.

Years 2 to 5 -1999 to 2002

Continue follow-up activities, analysis and reporting. Undertake special procedures to trace cases lost to follow-up, by direct contact of next of kin or home visits.

Year 6 - 3

Perform formal evaluation of the outcome of the intervention by comparing incidence and mortality from breast cancer in the screened and control cohorts.

Perform analysis of the risk of cancer at various sites in relation to reproductive history, tobacco and alcohol consumption and family history of breast cancer.

ANNEX 2

LIST OF PERSONNEL

Name	Post	Dates
Staff in Lyon, France		
Lorna Gibson	Scientist/Data manager	1996-97
Andy Cooke	Statistics assistant	1998
Ingunn Emery	Secretary	1999
Susan Anthony	Secretary	2000-2005
Nicolas Mitton	Computing Assistant	2000-2002
Kristina Ashton	Secretary	2003
Isabelle Battaglia	Secretary	2003
K. Lenormand	Computing Assistant	2004
Clarisse Hery	Postgraduate student	2004-2005
Eric Masuyer	Statistics assistant	2005
Field Staff, Philippines		
C. Ngelangel	Investigator	1995-6
M.G. Reyes	"	"
M.L. Munson	"	"
D. Esteban	Investigator	1995-2005
J. Ruzol		1999
C. Guanlao		1999
Ellen Marquez	Registry clerk	1997-2002
Evangeline Lucero	Clerk	1997-2002
J. Isla	Registry clerk	1999-2005
Portia de Guzman	"	2005
Elisha de Guzman	"	2005
C Romanillos		1999
W. Esguerra	C. Physician	"
R. Joson	"	1995-7
E. Tan	"	"
Agustina Abelardo	Pathologist	1996
Corazon Salvador	HC Coordinator	"
Maridina Dizon	"	"
Edwin de Guzman	"	"
Benjamin de Guzman	"	"
Aida Gatchalian	"	"
Susan Ong	"	"
Catherine Carlos	"	"
Josefina Bacuen	"	"
Concepcion Rivera	"	"
Cecilia dela Paz	"	"
Erwin Advincula	"	"
Marissa Ricardo	"	"
Jesusa Alcantara	"	"
Aurora Cruz	"	"
Cornelio Carandang	"	"
Aurora Tinio	"	"
Herminia Cipriano	"	"
Erlinda Roxas	"	"
Marie Fe Lavarias	"	"

Milagros Pasion	“	“
Julie Daniel	“	“
Julio Garcia	“	“
Ma. Socorro Baluyot	“	“
Donna Salmos	“	“
Loreto Tajonera	“	“
	Facilitators	
	Health workers	
Abigail Bautista-Gines	Supervisor/Data Manager	1997-2003
Teresa Malabanan-Medes	Data encoder	1997-2002
Herly Sy	“	2005?
Florenda Vallespin	Office staff	1996-7
Ricardo Barlaan	Clerk	“
Bonifacio Aragona Jr	Driver	1996
Joel	Janitor	1996
Corazon Ngelangel	Office staff	1997-8
Cristina Santiago	Clerk	1996-8
Josaly Calcitas	Office staff	“
Marilou Daliston	“	“
Nenita Marasigan	“	“
Vilma Matias	“	“
Linda Pedrasa	“	“
Noreza Costibolo	“	“
Malou Matsuda	Study doctor	1997
Bert Roxas	“	“
	4 Comelec list pickers	1996
Shiela Prila	Nurse supervisor	1997
Gloria Corpuz	Nurse	1996
Rechie Barayoga	“	“
Lanie Cabantog	“	“
Harmanie Asuncion	“	“
Madelaine Estopacio	“	“
Cecille Lado	“	“
Gerly Medina	“	“
Lina Obana	“	“
Nora Sabrosa	“	“
Rodalyn Vicuna	“	“
Arlene Villamor	“	“
Rowena Quintana	“	“
Lourdes Yeban	“	“
Carmelita Zarco	“	“
Mary Jane Saron	“	“
Mercia Cualon	“	“
Divina Surigao	“	“
Merly Francisco	“	“
Leazel Tulang	“	“
Vilma Matias	“	“
Marilou Dalistan	“	“
Donna Marie Mica	“	“
Joan Aguinaldo	“	“

Kathleen Aguilar	“	“
Guadalupe Morales	“	“
Franzaida Cortez	“	“
Julia Reyes	“	“
Fritzie Solomon	“	“
Jennifer Jamera	“	“
Mary Vic Sedamo	“	“
Pamela Sandoval	“	“
Mayleen Kee	“	“
Nenita Marasigan	“	“
Rosa Maria Sayson	“	“
Julita Reyes	“	“
A.V. Laudico	Consultant, Philippines Cancer Society	1999-2004
Francisca P. Cuevas	HC Coordinator	2005
Maria-Rica Mirasol-Lumague	Investigator	2005-7
Jane C. Baltazar	“	2005
Janelle Palma	Data entry operator	2005
Victoria Medina	Field coordinator	2005
Constancio Saludez,	Administrative assistant	2005
Armalyn Carinal	Nurse	2005
Dyan Grace Decastillo	Nurse	2005

ANNEX 3

Abstract for the Era of Hope meeting, Washington DC, October/November 1997

BREAST CANCER SCREENING BY PHYSICAL EXAMINATION: A RANDOMIZED TRIAL IN THE PHILIPPINES

D. Maxwell Parkin[1], Corazon Ngelangel[2],
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INTRODUCTION. Primary prevention programs to reduce the incidence of breast cancer (BC) are not feasible due to our poor understanding of the causes of the disease. A much greater impact on mortality from breast cancer is achievable through screening programs which lead to detection of cancers which are smaller, at an earlier stage, and less malignant than those which surface clinically. However, population screening programs by mammography require extensive provision of expensive technology and highly trained radiologists and radiographers. The cost per life-year saved is therefore relatively high and clearly an inappropriate use of health care resources for many countries.

The alternative screening strategies which have been proposed are physical examination of the breasts (PE) and breast self-examination (BSE). The efficacy of either procedure has not as yet been assessed in a proper experimental setting.

Purpose of the project is to establish 1) whether a program of mass screening by PE performed by trained medical personnel can be set up in a developing country as part of the routine activity of first level health services, and 2) whether and to what extent such a program can reduce mortality from breast cancer. The location is Metro Manila and Rizal Province of the Philippines.

STUDY DESIGN. The study is a randomised controlled trial of the effect of annual PE of the breasts performed by trained nurses/midwives, in reducing mortality from breast cancer. The study area comprises the central, more urbanized municipalities of the National Capital Region. In 1990, the estimated size of the female population aged 35-64 was about 340,000. The units of randomisation are the 202 health centers (HC's) serving the study area.

Women aged 35-64 years resident in the intervention HC areas are offered 5 annual breast examinations, carried out by trained specialized nurses. Women in the control area receive no active intervention, but are exposed to the general health education campaigns carried out by municipal authorities and voluntary bodies. Examiners are trained making use of breast silicon models. At first visit women are interviewed to record demographic variables and risk factors for breast cancer. Instruction in BSE is given and PE performed. Demographic characteristics of women who refuse PE are also recorded. Women with detected abnormalities are referred for final diagnosis to special clinics made available in 3 major hospitals staffed by project personnel.

RESULTS. During 1995 a coordinating center has been set up. HC's were randomised to intervention and control arms. Hospital clinics for referral of positive women and mechanisms for documentation of results including questionnaires and forms have been established. Nurses were recruited and trained. Data processing was organized. The intervention is fully operational since

March 1996. Lists of the eligible population. Printouts of electoral rolls have been obtained recently. They have been computerized and are regularly matched with the lists of women examined by automatic record linkage. Follow-up: procedures in the two cancer registries serving the study populations (Manila-PCS and Rizal DOH) have been improved, so that general case finding is taking place in a more timely manner than previously.

Keywords: Screening, Prevention, Randomized Trial, Physical Examination, Philippines

This work was supported by the U.S. Army Medical Research and Material Command under DAMD17-94-J-4327.

Accomplishments at 1/1/97: a total of 105 106 were offered the examination, 80 026 (76%) accepted both interview and PE. Two-thousand and ninety-nine women were positive for a suspect lump (2.6% of those examined); 448 of these attended a clinic for further clinical investigation (compliance with referral 21.3%); 307 (14.6%) had a definitive diagnosis. Of the 307, 13 had malignant breast cancer (4.2%).
The characteristics of compliers and refusers of PE were compared. Contrary to what is usually observed in western countries, refusers were of higher social class.
Action was taken to improve compliance with clinical investigation among women detected positive. One thousand of the positive women who did not comply with clinical investigation were visited a second time to assess the motives of non-referral. They survey indicates that the main reasons of non-compliance are inconvenience and costs. Medical teams formed by a doctor and a nurse and equipped to perform need biopsies, were then sent to visit non-compliers at their home in order to obtain a final diagnosis. This activity has been organized in the beginning of 1997 (recruitment and training of doctors) and is currently on-going. The outcome of this initiative will be known in the next few months.
CONCLUSION. The experience of the first two years of field activity indicates that a screening program by PE can reach a higher coverage in this urban population. Positivity rate (2.6%) is sufficiently low to make the intervention cost-effective provided that positive predictive value and sensitivity of the test will prove high. However, the potential of the intervention is seriously compromised by the very low rate of compliance with referral of women detected positive at PE. Provision to reimburse diagnosis expenses have been made as part of the intervention. It appears that this mechanism is not sufficient to compensate for loss of working days. The project is now bringing the diagnostic facilities to positive women; it is hoped that the relatively few affected by malignant cancer will have a strong motivation to seek medical care.

No publications related to the project as yet.

Abstract for the Era of Hope meeting, Atlanta, June 2000

BREAST CANCER SCREENING BY PHYSICAL EXAMINATION: A RANDOMIZED TRIAL IN THE PHILIPPINES

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INTRODUCTION. Primary prevention programs to reduce the incidence of breast cancer (BC) are not feasible due to our poor understanding of the causes of the disease. A much greater impact on mortality from breast cancer is achievable through screening programs. However, population screening programs by mammography require extensive provision of expensive technology and highly trained radiologists and radiographers therefore they are an inappropriate use of health care resources for many countries.

The alternative screening strategies which have been proposed are physical examination of the breasts (PE), and breast self-examination (BSE). The efficacy of either procedure has not as yet been assessed in a proper experimental setting.

Purpose of the project is to establish 1) whether a program of mass screening by PE performed by trained paramedical personnel can be set up in a developing country as part of the routine activity of first level health services, and 2) whether and to what extent such a program can reduce mortality from breast cancer. The location is Metro Manila and Rizal Province of the Philippines.

STUDY DESIGN. The study is a randomised controlled trial of the effect of annual PE of the breasts performed by trained nurses/midwives, in reducing mortality from breast cancer. The units of randomization are the 202 health centers (HC's) serving the study area.

RESULTS. A single screening round have been completed in December 1997. The women offered PE are 154,000, of whom 91% were interviewed and examined. The number of women positive for a lump is 3,492 (2.4%). Only 21% of the positives referred to tumor clinics set up for the project, for further investigation. Active clinical follow-up of the others was completed by May 1998. Forty-two percent of them actively refused clinical investigation. By July 1999, 307 (14.6%) had a detinitive diagnosis. Of them, 33 had malignant breast cancer (4.2% prevalence rate).

This work was supported by the U.S. Army Medical Research and Material Command under DAMD 17-94-J-4327.

Follow-up of the cohorts has been organized through the population-based cancer registries and death certificates. Procedures to computerize the data collected have been established and regular data entry ensured. The following files have been created and are being maintained:

- Master file of women examined. It provides identification of the women, data on risk factors obtained by interview and outcome of physical examination. Data entry completed in June 1998.
- File of women positive for a lump and referred for further clinical investigation. Contains aIl information on diagnostic procedures performed and their outcome. Completed in June 1998.
- Nominal lists of the population resident in the intervention and control areas in May 1997. Data entry is complete, checks for duplicates is ongoing.
- File of the outcome of first and second screen-examinations for a sample of over 5,000 women who were screened twice. It is being updated with the results of the second examination.
- File of aIl incident breast cancer cases in the target population. Updated regularly with the new cases detected by the cancer registries.
- File of death certificates mentioning cancer. Periodically updated.

A software pro gram was developed in Lyon for the purpose of identifying records pertaining to the same woman. The program makes use of the usual basic demographic items - names and surname, date of birth, age and detailed address - and allows for differences in spelling or variations in the reported date of birth. Each variable contributing to the matching process is assigned a weight, which summarizes its discriminating power and the likelihood that it is reported incorrectly. The resulting matching score allows linkage of records within the same file (e.g. two screens of the same woman) or in different files.

A random sample, stratified by age, of 1,000 women resident in the control areas have been interviewed according to the same questionnaire used for the intervention. This will allow us to compare the characteristics of this cohort with those of the intervention group as a check on the randomization procedure.

The master file of the cohort of women examined is being matched with the list of the population resident in the intervention areas in May 1997. This process will output a cohort of unexamined women who were eligible for examination who either refused it or were not reached by the intervention. The comparison of breast cancer incidence in screened and unscreened subgroups of the intervention cohort will provide an indication of the effect of selection bias.

A shift in the distribution of stage at diagnosis towards earlier disease has been observed in cases diagnosed in the years when the intervention was carried out. Whether this is the result of the intervention is too early to tell but could be an indication of a potential positive impact of PE if accompanied by appropriate treatment.

Abstract for the Era of Hope meeting, Florida, September 2002

BREAST CANCER SCREENING BY PHYSICAL EXAMINATION: A RANDOMIZED TRIAL IN THE PHILIPPINES

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INTRODUCTION. Population screening programs by mammography require extensive provision of expensive technology. Alternative screening strategies are physical examination of the breasts (PE), and breast self-examination (BSE). The efficacy of PE alone has not as yet been assessed in a proper experimental setting. Purpose of the project was to establish 1) whether a program of mass screening by PE performed by trained paramedical personnel can be set up in a developing country as part of the routine activity of first level health services, and 2) whether and to what extent such a program can reduce mortality from breast cancer.
STUDY DESIGN. The study is a randomised controlled trial of the effect of annual PE of the breasts performed by trained nurses, in reducing mortality from breast cancer. The location is Metro Manila and Rizal Province, Philippines. The target population were women aged 35-64. The units of randomization were the 202 health centers (HC's) serving the study area.
RESULTS. A single screening round have been completed in December 1997. The women offered PE are 154,000, ofwhom 91 % were interviewed and examined. The number of women positive for a lump is 3,492 (2.4%). Only 21 % of the positives referred to tumor clinics set up for the project, for further investigation. Active clinical follow-up of the others was completed by May 1998. Forty-two percent of them actively refused clinical investigation. By July 1999, 307 (14.6%) had a definitive diagnosis. Of them, 33 had malignant breast cancer (4.2% prevalence rate). Follow-up of the cohorts was organized through the population-based cancer registries and death certificates.
Incident cases in the study population that occurred in 1995-99 were identified. No difference in the distribution of stage at diagnosis was observed in cases diagnosed in the two study cohorts. Risk factors for breast cancer were analysed by the nested case-control design. The incidence of breast cancer was 3 times greater in nulliparous compared with parous of 6 or more full-time pregnancies (RR=3.3, 95%cl1.6-6. 7). Their risk was even greater when compared with those who had their first child before age 19 (RR=4.8, 95%cl1.8-13.2). These results are in agreement with the literature.

This work was supported by the U.S. Army Medical Research and Material Command under DAMD17-94-J-4327.

Abstract for the Annual Meeting of the International Association of Cancer Registries, Beijing, China, September 2004

TREATMENT PRACTICES FOR BREAST CANCER IN MANILA

Laudico AV, Mapua CA, Pisani PP
PCS Manila Cancer Registry & IARC

Introduction Around 1995 the incidence of breast cancer in the female population of Manila was 57.4/100,000 (world standardised), the highest in Asia excluding Israel and even higher than in some areas of Southern Europe. Since early breast cancer can be treated effectively we conducted a descriptive study of the treatment regiments that are provided

Materials and Methods Source data were obtained from the data set of the PCS-Manila Cancer Registry. Breast cancer cases incident in 1991, 1994 and 1997 were selected. After exclusion of cases recorded on the basis of the death certificate only, and of those registered as metastatic at diagnosis (summary stage routinely recorded by the registry), we drew a random sample of 992 cases. An abstract form was prepared to collect information on diagnostic procedures, TNM stage, and treatments received separated into surgery, radiotherapy, adjuvant chemo and hormonal therapy. Dates of first administration and the names of the treating doctors were also abstracted. Medical records of all the cases were reviewed first. Treating doctors were then contacted by one of the authors (AL) to obtain complementary information, particularly on the use of adjuvant therapies that are often administered in private practices.

Results The 992 cases were almost equally distributed in the three incident years of interest (301, 342 and 349 respectively). Forty cases were advanced at diagnosis and therefore excluded, and no clinical information could be traced for 207 (21%) leaving a total of 745 cases, of whom 98% were microscopically verified.
Staging. 99% of the cases received a chest x-ray and less than 4% received in addition computerised tomography, liver ultrasound or bone scan examinations. Stage was not assessed for 5% of the cases. Ten percent were stage I; 31%, IIA; 29%, IIB; 26% stage III. This pattern was constant in the three years considered.
Treatment. 97% of the cases received radical mastectomy irrespective of stage at presentation. Only 17% of the cases received radiotherapy and the proportion increased steadily from 8% in stage I to 27% in stage IIIB. On average 53% received adjuvant chemotherapy; the proportion treated was higher in women below 50 years of age (55%) and declined to 35% in cases aged 60 or more. There was not a systematic association with stage at presentation.
Finally, tamoxifen treatment was administered to 51% of the cases with a significant inverse association with age (57% of cases below 50 years were treated *vs.* 42% in age group 60+ years). We also observed a trend towards an increasing proportion of treated cases with stage becoming more serious: 39% of stage I *vs.*58% in stage 3B. The use of hormonal treatment almost doubled between 1991 and 1994 and remained stable thereafter.

Conclusions. We have shown in previous studies that still too many cases of breast cancer present at diagnosis with advanced disease. With this work we show that standard treatment for non-advanced cases is sub-optimal. In a country with limited resources to control cancer, interventions to improve and generalise access to optimal treatment for tumours that are potentially curable, would be cost-effective and should be of high priority.

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Outcome of screening by clinical examination of the breast in a trial in the Philippines

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The value of screening by Clinical Examination of the Breast (CBE) as a means of reducing mortality from breast cancer (BC) is not established. The issue is relevant, as CBE may be a suitable option for countries in economic transition, where incidence rates are on the increase but limited resources do not permit screening by mammography. Our aims were to assess whether mass screening by CBE carried out by trained para-medical personnel is feasible in an urban population of a low-income country, and its efficacy in reducing BC mortality. Our study was designed as a randomised controlled trial of the effect on BC mortality of 5 annual CBE carried out by trained nurses. The target population was women aged 35–64 years, resident in 12 municipalities of the National Capital Region of Manila, Philippines. The units of randomization were the 202 health centres (HC) within the selected municipalities. During 1995 nurses and midwives were recruited and trained in performing CBE. The first round of screening took place in 1996–1997. The intervention however showed a refractory attitude of the population with respect to clinical follow-up and was discontinued after the completion of the first screening round. Cases of breast cancer occurring in the study population during 1996–1999 were identified by the 2 local population-based registries. In the single screening round 151,168 women were interviewed and offered CBE, 92% accepted (138,392), 3,479 were detected positive for a lump and referred for diagnosis. Of these only 1220 women (35%) completed diagnostic follow-up, whereas 42.4% actively refused further investigation even with home visits, and 22.5% were not traced. Of 53 cases that occurred among screen-positive women in the 2 years after CBE only 34 were diagnosed through the intervention. Eighty cases occurred among screen-negative women. The test sensitivity for CBE repeated annually was 53.2%. The actual sensitivity of the programme was 25.6% and positive predictive value 1%. Screen-detected cases were non-significantly less advanced than the others. Previous studies have shown that most breast cancer cases in the Philippines present at advanced stages and have an unfavourable outcome. Although CBE undertaken by health workers seems to offer a cost-effective approach to reducing mortality, the sensitivity of the screening programme in the real context was low. Moreover, in this relatively well-educated population, cultural and logistic barriers to seeking diagnosis and treatment persist and need to be addressed before any screening programme is introduced.

Key words: mass screening; breast clinical examination; female breast cancer; Philippines

In the year 2000 breast cancer accounted for over 1 million new cases per year worldwide; it is the most common cancer in women, and incidence rates are rising in low-risk countries.[1] These trends are likely to continue, because the current pattern of later childbearing, decreasing fertility, increasing height and weight and 'westernization' of diets will all be associated with increased risk.

Significant improvements in the prognosis of early breast cancer have been achieved in the 1980s and 1990s[2,3] and have substantially contributed to the initial reduction of mortality observed in some high-risk countries.[4–7] For treatment to be highly effective however, it is essential that the disease is detected at an early clinical stage.

Possibly because of the low burden relative to other diseases, cancer awareness in low-risk developing countries is generally poor. Cases tend to present at an advanced stage and have an unfavourable outcome. This may induce a general sort of pessimism in the medical community about the capacity of the health system to impact on cancer prognosis even for sites that can be successfully treated. Such pessimism is not justified because even when resources are limited, at least 60% of breast cancer cases presenting with disease localised to the breast survive 5 years from diagnosis.[8] A shift toward a more favourable distribution of stage would therefore have a significant impact on mortality.

Our study tests the feasibility and the effect of systematic screening of the population by clinical breast examination (CBE) on stage at presentation and ultimately on breast cancer mortality, in the urban area of Manila, the Philippines. This was done where the 2 local cancer registries had reported relatively high incidence rates (an age standardised rate of 48.7 per 100,000 in 1993–1997[9]), and over 60% of the cases were at Stage III or VI at diagnosis.[8] Our study was designed as a randomised trial and was planned to involve 5 rounds of screening for women in the intervention group, at intervals of 1–2 years.

We describe the study population, the intervention and its results in terms of breast cancer detection, cumulative incidence in 3 years of follow-up in the group examined and sensitivity and specificity of the examination in that setting. Due to a very low compliance with clinical follow-up, however, the intervention ceased after completion of the first round of examinations. We discuss reasons for the outcome and implications for the development of cancer control plans in developing countries.

Material and methods

Study design

Our study began in 1995. It was designed as a randomised controlled trial of the efficacy of five annual clinical examinations of the breasts carried out by trained nurses/midwives, in reducing mortality from breast cancer. Women 35–64 years of age, resident in the 12 central, more urbanized municipalities of the National

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Capital Region of Manila were the target population. Young women were included because of the high proportion of cases below age 50.[9] In 1990, the estimated size of the female population 35–64 years of age was about 340,000. The units of randomization were 202 health centres (HC) within the selected municipalities. These were randomly assigned to intervention or control arm by block randomization. Blocks were defined based on population size and a deprivation index indicating the presence of squatters areas within the administrative borders.

Identification of the eligible population

Lists of women resident in the 12 municipalities and who were included in the electoral rolls were obtained from the Department Of Health (DOH). Women were identified by family and first name, date of birth and complete address (street and administrative area that coincided with the area served by a health centre). Electoral rolls had last been updated during 1994–95.

Intervention

In the first year (1995) a coordinating centre was set up. Nurses and midwives were recruited and trained in the technique of CBE using the MAMMACARE^{TM10} programme tested previously in the Philippines, that uses silicone models of the breast for training purposes[11] and has been shown to enhance performance of examiners in previous studies.[12–14] Training was repeated for selected groups of examiners who missed or over-reported by 20% the lumps in the silicone models.

The first round of examinations took place in 1996–97 (24 months) and included 151,168 women. Eligible women resident in the intervention HC were contacted in 2 ways: at the HC among those women who were attending for a variety of reasons, and, for those who did not, by systematic home visits. Basic demographic characteristics (age, marital status, socio-economic level) of eligible women were recorded and the nature and purpose of the intervention were explained. Women were asked to give a signed assent to participation. They were interviewed and CBE was carried out by the trained examiners. The interview addressed socio-demographic variables and classical risk factors for breast cancer. Women were also instructed in the technique of breast self-examination (BSE) and provided with a leaflet in the local language explaining the purpose and methodology of BSE.

Women in whom abnormalities were detected and classified ''positive'' for a suspected lump were referred for diagnosis to special clinics established in 3 major hospitals and staffed by project personnel. The costs of transport to the clinic and of all medical procedures required to reach diagnosis were covered by the project. In addition, in the last year of the intervention period, a mobile team, comprising a doctor and a nurse and equipped to perform needle biopsies, carried out home visits for all positive women who had not reported to the referral centre, to obtain a final diagnosis. The standard diagnostic process consisted in a physical examination by a specialist doctor followed by fine needle aspiration or excision biopsy if indicated. Mammography was not available to the large majority of the women judged positive.

Women in the control area received no active intervention but were exposed to the general health education campaigns carried out by municipal authorities and voluntary bodies.

Follow-up

The aim of the follow-up of the intervention and control cohorts was to identify women who developed breast or other cancers, those who died and those who migrated outside our study area.

Two cancer registries, Manila-PCS and Rizal-DOH,[9] covered the study population. Together they serve the whole metropolitan area and the surrounding more rural province of Rizal. The case-finding procedures of both registries were enhanced to reduce time to registration. New abstract forms including detailed information on extent of disease, tumour size, spread and nodal involvement were adopted. All registered cases of breast cancer were followed-up to 2001 to assess their vital status. Hospital records were first reviewed, and treating doctors and the cases' families were contacted to complement this information.

In a pilot study we tested the feasibility and reliability of active collection of death certificates (for all causes of death) for linkage with the study cohort. Mortality rates computed from the information thus obtained were however unrealistically low and cancer was over-represented. This activity was therefore abandoned, and only cancer deaths continued to be recorded, as part of the usual routine of the cancer registries. Breast cancer cases and deaths identified during the follow-up period were linked with the master file (interviews and CBE results) using a probabilistic record linkage software 'RECLINK'.[1] Uncertain matches were sorted out by the registries' directors after consultation of paper documents.

All matched cases were retained as incident if date of diagnosis recorded by the registries occurred after date of interview/examination.

Data analysis

The main outcome measures are the number and cumulative incidence of breast cancers in the cohort of interviewed women. Because only one screening round was carried out, sensitivity, specificity and predictive value were calculated using as gold standard the incident cases identified by the registries in 2 years from screening examination, including those diagnosed at the time of testing. Additional parameters describing the performance of the intervention are presented as absolute and relative frequencies, means and their standard deviations (SD) and 95% confidence limits (CI). Because of the large numbers of subjects involved, statistical testing was avoided when comparing examined and refusers. Confidence limits of proportions are based on the exact binomial distribution. Differences between proportions adjusted for age were tested by the Mantel-Haenzel procedure.

Results

Intervention

The number of women interviewed and offered CBE was 151,168; 8% of these women refused to be examined. Table I shows some socio-demographic characteristics of the 2 groups as assessed at interview, women interviewed and examined, and women interviewed who refused CBE. The 2 groups were very similar in age, 44.8 $\pm$ 8.2 years and 44.7 $\pm$ 8.4 respectively, and were also of similar age at menarche, between 13.6 and 13.4 years, but differed for other variables. Refusers were 1 year older at their first full-term pregnancy and of higher socio-economic status than compliers (as shown by the proportion of women who attended college [18% *vs.* 12%] and the proportion illiterate [6% *vs.* 18%]), had a significantly greater income (means were Pesos 1,556/month/cohabitants *vs.* 10,800), were more often nulliparous (17% *vs.* 10%) and less likely to have had 5 or more children (25% *vs.* 33%).

A total of 3,479 women (2.5% of those examined) were judged to have a lump and were referred to the project clinics (Table II). Of these, 1,293 (37.2%) received further investigation, and complete diagnostic follow-up was achieved for 1,220 women, 35% of those positive on screening. A total of 1,475 women (42.4%) actively refused further investigation, even with a home visit, and 784 of the non-compliers (22.6%) were not traced, and were either reported by the neighbours, or assumed, to have moved away or died.

[1]RECLINK is a record linkage software developed at unit of Descriptive Epidemiology, International Agency for Research on Cancer, Lyon. The software performs probabilistic linkage between records from different sources using selected personal identifiers (names, date of birth, sex, address).

TABLE I – COMPARISON OF CHARACTERISTICS OF WOMEN EXAMINED AND INTERVIEWED WOMEN WHO REFUSED EXAMINATION

	Compliers N = 138,392	Refusers N = 12,776
Age in years (mean ± SD)	44.8 ± 8.2	44.7 ± 8.4
Illiterate (%)	18.0	6.2
Attended college/university (%)	12.3	17.7
Monthly income (pesos) mean ± SD	5744 ± 5590	10806 ± 12023
Income/No. of cohabitants (pesos)	1556 ± 1713	2748 ± 3292
Mean age at menarche	13.6 ± 1.7	13.4 ± 1.5
Mean age at first full-term pregnancy	23.0 ± 4.5	24.1 ± 4.5
Nulliparous (%)	10.3	16.6
Women with 5 or more children (%)	32.6	25.3

TABLE II – RESULTS OF THE SINGLE ROUND OF SCREENING, AND CLINICAL OUTCOME AFTER 2 YEARS OF FOLLOW-UP

Parameter	*n* (%)	Cancers diagnosed by screening
Number of women interviewed:	151,168	
Number of women examined:	138,392 (91.5)	
Number positive on screening:	3,479 (2.5)	
Completed diagnostic follow-up	1,220	34
at project clinics	556	21
at project clinics	73	1
at project clinic after home visit	590	12
Refused or follow-up incomplete	1,475	
Not traced	784	
Total	3,479	

Among the 1,220 women who completed diagnostic follow-up, 34 malignant cancers were detected; the presence of a lump was not confirmed in 563 (46.1%) and 623 (51.1%) were diagnosed as having benign breast disease.

Because of the poor compliance with follow-up of screen positive women, even with home visits, the active intervention was discontinued after completion of the first screening round in December 1997.

Proportion positive by selected personal characteristics

Among examined women the positivity rate decreased constantly with age from 2.9% in women below 40 years to 1.5% in women aged 60 or more (Table III). The percentage of women detected positive was higher in those with <3 pregnancies (3.3% *vs*. 2.2%). The positivity rate was not consistently associated with the level of education and was higher in women reporting low income. It ranged from 1.1 to 6.0% in the 12 municipalities. Rates above the average were recorded in the more affluent areas of Makati (4.0%), Mandaluyong (6.0%) and Malabon (3.9%). The high rate of positives among women with missing information, in particular on education level, is an interviewer effect. We observed an inverse association between total number of interviews and examinations carried out per nurse and both their referral rate, and the rate of missing answers in their interviews. In other words, the less experienced the poorer the performance.

Follow-up

After exclusion of cases whose incidence date preceded date of recruitment, there were 133 breast cancer cases, incident within 2 years of enrollment linked with records of women in the intervention cohort (Table IV). The cumulative incidence of breast cancer was 9.6/10,000. Eighty of these cases had been judged negative on CBE, corresponding to a cumulative incidence of 5.4 new cases per 10,000 screen-negative women.

Fifty-three cases were detected among the 3,479 women who were screen-positive (152.3/10,000), 38 of which were detected through the screening process among women reporting for the follow-up (diagnostic) examination (311.5/10,000). Fifteen (15) cases occurred among those women who did not complete the diagnostic process (66.4/10,000): of these, s6ix were refusers (40.6/10,000) and 9 were lost to follow-up (114.8/10,000). Thirty of 38 screen-positive cases were diagnosed within 12 months of the first examination, and 8 were diagnosed later. Of these late cases of cancer, 4 were found in women who were positive on CBE, but in whom the lesion was judged to be non-malignant at diagnostic follow up (2 by CBE carried out by the specialist doctor and 2 by fine needle biopsy).

Of 15 cases identified among refusers 11 occurred within a year and 4 later. The 80 cases diagnosed among screen-negative women were almost equally distributed between the 2 periods.

Test sensitivity

If we generously allow that every positive examination in a woman who eventually proved to have cancer (within 2 years of the test) is a true positive, then the test sensitivity for annual CBE was 53.2% and the positive predictive value was 1.2%. Specificity was virtually 100%. The test sensitivity decreased to 39.8% (53/133) for one CBE carried out in 2 years. Only 34 cases were actually diagnosed through the intervention reducing test sensitivity to 25.6% and positive predictive value to 1.0% (34/3,479).

Table V shows the distribution by age of clinical extent of the disease in the 34 cases diagnosed by the screening process and in the other 99 cases identified in the examined cohort 80 cases screen-negative, 15 lost to diagnostic follow-up or refusers and 4 diagnosed as having benign disease. None of the screen-detected cases had distant metastasis at presentation whereas 17% of the others had metastatic disease ($p = 0.032$ 2-sided test of the difference between the 2 proportions). The proportion of advanced cases increased with increasing age from 12% below 45 years to 27% at age 55+ years (test for trend, $p = 0.037$). Of the staged cases classified benign originally, 2 of 3 presented with distant metastasis.

Discussion

Breast cancer is a growing problem in developing countries. Increases in incidence and mortality are widespread and often more marked in younger generations of women.[1,5,6] In populations of South-East Asia increases range from 1 to 3.6%.[15–18] Mortality of cancer cases and breast cancer cases in particular is unnecessarily high.[8] Known risk factors are linked to reproductive history and lifestyle and are hardly modifiable, rather they are likely to become more prevalent with economic development. In these circumstances, interest has tended to focus upon early diagnosis and treatment, as a means of reducing at least mortality.[19–21]

The efficacy of breast self-examination has been formally tested in a randomised trial in Shanghai, China.[22] No significant reduction of breast cancer mortality in the intervention group was

TABLE III – PROPORTION POSITIVE WOMEN PER 10,000 EXAMINED, BY SELECTED PERSONAL CHARACTERISTICS

	No. positive	No. examined	Positives/10,000
All	3,483	138,392	
Age			
< 40	1,356	46,896	2.9
40–49	1,443	53,459	2.7
50–59	538	28,470	1.9
60+	145	9,543	1.5
Missing	1	24	4.2
Education			
Max primary	925	59,803	1.5
Max secondary	997	50,221	2.0
College+	312	17,072	1.8
Missing	1,201	14,452	8.3
Full-term Pregnancies			
< 3	1,302	39,777	3.3
3+	1,920	87,562	2.2
Missing	261	11,053	2.4
Monthly income per No. of cohabitants			
Low	1,679	60,799	2.8
High	1,031	57,998	1.8
Missing	674	19,595	3.4

TABLE IV – BREAST CANCER CASES THAT OCCURRED AMONG SCREENED WOMEN, BY STAGE AT DIAGNOSIS AND SCREENING OUTCOME

	Unknown No (% of total)	Localised	Regional	Distant	Total known stage
Age < 45 years					
Screen-detected	5 (50)	–	5 (100)	–	5
Other cases[a]	3 (10)	7	16 (62)	3 (12)[b]	26
Age 45–54 years					
Screen-detected	6 (35)	2	10	–	12
Other cases[a]	5 (12)	6	22 (61)	8 (22)[b]	36
Age 55+ years					
Screen-detected	4 (60)	–	2 (100)	–	2
Other cases[a]	7 (24)	4	12 (55)	6 (27)[b]	22
All ages					
Screen-detected	15 (44)	2 (11)	17 (90)	(0)[c]	19
Other cases[a]	15 (15)	17 (20)	50 (60)	17 (20)[c]	84

[a]Screen-negative or screen-positive lost to follow-up or screen-positive benign disease.–[b]Test for trend in the prevalence of advanced cases by age: $p = 0.037$.–[c]Difference in the prevalence of advanced cases, screen-detected vs. other cases: $p = 0.032$.

TABLE V – BREAST CANCER CASES (BC) IDENTIFIED IN THE INTERVENTION COHORT (TOTAL 138,392) IN 2 YEARS OF FOLLOW-UP, BY SCREENING OUTCOME AND TIME SINCE CBE

	Number of women	No. incident BC in first 12 months	No. incident BC in more than 12 months	No. incident BC all	No. of cases per 10,000 examined
All women examined	138,392	77	56	133	9.6
Screen-negatives, all	134,913	36	44	80	5.4
Screen-positives, all	3,479	41	12	53	152.3
Screen-positives by screening outcome:					
Refusers and lost:	2,259	11	4	15	66.4
Compliers:	1,220	30	8	38	311.5
Malignant breast cancer	34	30	4	34	
No mass or benign breast disease	1,186	–	4	4	33.7

Test sensitivity for annual examination; 41/(36 + 41) = 53.2% (95% c.i. 41.5%–64.7%).–Test sensitivity for biennial examination; 53/(80 + 53) = 39.8% (95% c.i. 31.5%–48.7%).

detected after 10 years of follow-up and the distributions of stage at diagnosis in screen and control groups were very similar. The small size of the lesions diagnosed in the control subjects in this trial (47 % ≤2 cm diameter, 48% node negative), however, suggests a high level of health-awareness in this special subset of the Shanghai population, and may give little scope for improvement in outcome through early detection by BSE.

Clinical breast examination carried out by a trained examiner has many attractions. In programmes where it is combined with mammography, CBE finds fewer lesions but does detect some that had been missed by mammography. In general the differential is less for younger women.[23] In the CNBSS II trial of women ages 50–59, there was no significant difference in the efficacy of CBE alone compared to CBE combined with mammography.[24] CBE has been introduced as a single screening modality in Japan. There is some suggestion that, where coverage by such screening is high, breast cancer mortality rates have declined more than in other areas,[25] although a case-control study was inconclusive.[26] Manpower requirements for a screening programme based on CBE would be expensive but in many developing countries these are generally easier to mobilize, than the technology required for mammography. Based on these arguments, it has even been suggested that CBE would be a more cost-effective alternative to screening women at high risk, in low-income countries.[27]

The trial in Manila was designed to assess whether a meaningful reduction in mortality from breast cancer could be achieved in a developing country using an inexpensive procedure and locally available resources, that is physical examination of the breast carried out by nurses and midwives. The mortality reduction that was aimed for, among the women actually screened and followed-up, was 25%, a smaller effect than that of mammography that had been demonstrated in randomised controlled trials (RCT) settings to reduce mortality by about 30–35% among screened women, and probably the minimum mortality reduction that would be worthwhile in any future programme. The Manila area was selected for the trial for several reasons, the relatively high incidence of breast cancer; the availability of treatment facilities (surgery, radiotherapy and systemic therapy are provided by both the public and private service); and the possibility of recruiting a large number of qualified nurses to act as examiners.

The unexpected result that jeopardised the whole intervention was the unforeseen reticence of women found with abnormalities and informed of the implications to their life, to pursue diagnosis and treatment. These problems had in fact been noted during a pilot phase. In the main study they were addressed from the beginning by provision of free transport and consultation. This tactic was not sufficient, however, and a programme of diagnostic home visits was introduced. Even this failed to raise compliance with diagnostic follow-up beyond 35%. The reasons can only be speculative at this stage but deserve *ad hoc* studies. One may think that women did not understand the implications of undergoing CBE. This is a relatively educated population, however, and highly exposed to media messages. The observation that women who refused to enter the trial were of higher socio-economical level reinforces the notion that is not a lack of information the cause of non-action. Alternative hypothesis are also possible. Lack of trust in the health system and in one's chances to be cured may discourage action. Such attitude is not in contrast with accepting screening examination. In a recent survey in the United States, 60% of interviewed people reported they would wish to be examined for a cancer for which there is no hope of cure.[28] It is known that women attend for breast cancer screening in anticipation of a negative finding,[29] and screening is not a stressful procedure for those with a negative mammography.[30,31] Receipt of an abnormal result, however, is associated with considerable psychiatric morbidity,[32–34] and this may have played a role in the low level of compliance. The decision not to undergo investigation was a positive one in most instances, and not related to logistical or financial barriers. It is known that patient's decision making is not always apparently rational. Misinformation, denial, overconfidence, distrust and confusion may all play a role.[35]

The second major limitation highlighted by our study is the modest sensitivity of the screening test in the setting in which it was applied. Sensitivity and specificity of CBE have been measured in randomised trial of mammography and screening programmes, relative to new cases diagnosed within 12 months detected by either CBE or mammography and including interval cases. In these conditions the average sensitivity and specificity were 54% and 94% as estimated in the meta-analysis by Barton.[37] The sensitivity was higher (68%) in the Canadian trial in the control arm who received only CBE.[38] Sensitivity estimates are difficult to compare due to varying definitions of the reference gold standard in different studies. In our study the reference set included only cases that surfaced clinically within 12 or 24 months, the majority of which were relatively advanced (Table V). We would expect therefore an even lower estimate of the sensitivity had the cohort also been screened by mammography. We also showed that less experienced nurses performed more poorly. Though predictable this observation reinforces the need to form personnel devoted to this activity.

Our results reflect what might realistically be expected from CBE as a screening modality when applied by nursing personnel formally trained in the procedure but necessarily inexperienced. Clearly, if CBE is to be at all useful, a much greater effort in training and quality control of performance than was possible in the Manila trial will be required. But it is unlikely that this can be obtained from staff in primary health centres normally dealing with more common diseases. One could envisage a new professional profile of health workers who specialise in the diagnosis and follow-up of cancer and are made available regularly in health centres. Despite the modest performance observed of the clinical procedure we could document an improvement of stage at presentation among examined women. This justifies pursuing further studies based on CBE.

Conclusion

We show that in the urban population of Manila serious logistic as well as psychological barriers to seeking medical attention for breast cancer persist. An occasional contact with unknown health workers has a minimal impact on health-beliefs and behaviours. In addition, the sensitivity of CBE carried out by trained but inexperienced personnel is low. Yet, early diagnosis remains a high priority to improve the lamentable stage distribution that leads to premature death of a large number of cases.

Cancer awareness needs to be reinforced taking inspiration from the experience of high-risk countries[36] but bearing in mind the specific context where other diseases will continue to be of greater importance and governmental expenditure in health care is unlikely to increase substantially. Alternative organizational settings need to be devised and tested. Access to early diagnosis could be improved for instance by promoting detection of BC among health operators in first level primary care services that interact with the population on a daily basis. Cancer centres should be created to provide experienced personnel and appropriate diagnosis and treatment. Rotating breast clinics could then be organised on a regular bases within health centres for primary care, to teach and encourage BSE and to provide opportunistic CBE. The regular presence of specialised personnel could also help to raise awareness and trust.

In recent years research on means to improve cancer control when resources are limited has focused on the evaluation of low-cost screening procedures and our study is an example in this direction. The outcome of the Manila trial is a reminder however, that culturally-related health beliefs are a major obstacle to early diagnosis and that awareness and access need to be addressed in first place.

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